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EXAMINER
RAO, MANJUNATH N

ART UNIT	PAPER NUMBER
1652	9

DATE MAILED: 09/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/836,613	HOPWOOD ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-36,60-67,70,71,85 and 96-99* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-36,60-67,70,71,85 and 96-99* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 19-36, 60-67, 70-71, 85, 96-99 are currently pending and under consideration in this application.

Applicants' amendments and arguments filed on 6-9-03, paper No.8, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29 and 61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 29 and 61 recite the phrase "amino acids corresponding to human α-N-acetylglucosaminidase". The metes and bounds of the phrase, specifically to the sub-phrase "corresponding to" is not clear to the Examiner. It is not clear whether the above phrase means that the amino acid is identical to human enzyme or that it has the same number of amino acids or the same type of amino acids at same positions etc. A quick perusal of the specification did not yield a specific definition for the above phrase thus rendering the claim indefinite.

Claim 97 and claim 98 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject

matter which applicant regards as the invention. Claim 97 recites the limitation "mammalian" in line 1. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-36, 60-67, 70-71, 85, 96-99 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant enzyme having α-N-acetylglucosaminidase activity and an amino acid sequence SEQ ID NO:2 or an amino acid sequence that is 80% identical to SEQ ID NO:2 or an amino acid sequence that is encoded by a polynucleotide capable of hybridizing to SEQ ID NO:1 or 3 under high stringency conditions, having a molecular size of 79 to 89 kDa or a pharmaceutical composition comprising such enzymes, does not reasonably provide enablement for such an enzyme isolated from any or all sources having any molecular size, or such an enzyme having an amino acid sequence that corresponds to a human α-N-acetylglucosaminidase or fragments or derivatives of such enzymes, including mutants and variants and pharmaceutical compositions comprising the above enzymes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3)

the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 19-36, 60-67, 70-71, 85, 96-99 are so broad as to encompass any α-N-acetylglucosaminidase isolated from any or all sources, comprising an amino acid sequence that corresponds to a human α-N-acetylglucosaminidase or fragments or derivatives of such enzymes, including mutants and variants and pharmaceutical compositions comprising the above enzymes. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of recombinant α-N-acetylglucosaminidase broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still obtain the desired activity, requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of a single α-N-acetylglucosaminidase from a single source.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art

would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any recombinant α-N-acetylglucosaminidase because the specification does not establish: (A) regions of the protein structure which may be modified without effecting the glucosaminidase activity; (B) the general tolerance of any or all recombinant α-N-acetylglucosaminidases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid reside of any recombinant α-N-acetylglucosaminidase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including recombinant α-N-acetylglucosaminidases from all or any sources and with an enormous number of amino acid modifications of the α-N-acetylglucosaminidase with SEQ ID NO: 2. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of α-N-acetylglucosaminidase having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action, applicants have traversed the above rejection arguing that they have amended claim 19, 35 and 60 etc. to recite the activity of the enzyme and limited the per cent homology of the amino acid sequence to 80% in comparison to SEQ ID NO:2 and that the encoded amino acid is also limited to that encoded by a nucleic acid capable of hybridizing to SEQ ID NO:1 or 3 under high stringency conditions and therefore the rejection is not warranted. This argument is not persuasive to overcome the rejection because claims continue to be very broad and read on any or all recombinant N-acetylglucosaminidases irrespective of their source including other variants and mutants. While methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan producing enzymes as claimed by applicants requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. As previously stated the specification does not establish: (A) regions of the protein structure which may be modified without effecting the glucosaminidase activity; (B) the general tolerance of any or all recombinant α-N-acetylglucosaminidases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid reside of any recombinant α-N-acetylglucosaminidase with an expectation of obtaining the desired biological

function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Therefore the above rejection is maintained.

Claims 19-31, 35, 36, 60-66, 70-71, 96-98 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 19-31, 35, 36, 60-66, 70-71, 96-98 are directed to recombinant N-acetylglucosaminidase polypeptides and its fragments and pharmacological composition comprising the same. Claims 19-31, 35, 36, 60-66, 70-71, 96-98 are rejected under this section of 35 USC 112 because the claims are directed to a genus of polypeptides either drawn to N-acetylglucosaminidase polypeptides derived from SEQ ID NO:2 including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid residue in SEQ ID NO:2 and fragments of SEQ ID NO:2 that have not been disclosed in the specification. No description has been provided of the modified polypeptide sequences encompassed by the claim. No information, beyond the characterization of SEQ ID NO:2 has been provided by applicants which would indicate that they had possession of the claimed genus of modified polypeptides. The specification does not contain any disclosure of the structure of the polypeptide sequences claimed, including fragments and variants within the scope of the claimed genus. The genus of polypeptides claimed is a large variable genus including peptides which can have a wide variety of structure. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single

species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the previous Office action, applicants have traversed the above rejection arguing that possession of the invention may be shown by many ways and actual reduction to practice is one way. In summary applicants argue that they have disclosed sufficiently detailed relevant identifying characteristics such as complete or partial structure (e.g. SEQ ID NO:2 and sequences having 80% homology to SEQ ID NO:2), other physical and/or chemical properties, functional characteristics (N-glucosaminidase activity) coupled with a known or disclosed correlation between function and structure or some combination of such characteristics and have therefore demonstrated possession of the invention under written description requirements. Examiner respectfully disagrees with such an argument. While it is agreed that applicants have disclosed the function and structure in some claims, applicants have not done the same in the claims rejected above. As explained above, applicants have claimed the enzyme based only on the function without any description of the structure. Therefore, contrary to applicant's arguments, they have not met the written description requirement for the above claims. Therefore the above rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 19-20, 26-29, 32, 35-36, 85, 96, 99, are rejected under 35 U.S.C. 102(b) as being anticipated by Zhao et al. (American Journal of Genetics, 1995, Vol. 57: A185, Abstract 1059). This rejection is based on the public availability of a printed publication reporting the cloning of a mammalian DNA encoding alpha-N-acetylglucosaminidase (NAG) enzyme. This rejection is also based on the breadth of the claims as written.

Claims 19-20, 26-29, 32, 35-36, 85, 96, 99 of the instant application are drawn to a recombinant, α-N-glucosaminidase or a fragment or a derivative of the same, expressed n mammalian cells, wherein the mammalian cell is capable of N-glycosylating the enzyme, wherein the NAG enzyme is in a glycosylated form and has a molecular weight of at least 79kDa to 89kDa when determined by SDS/PAGE and wherein the amino acid sequence of the NAG is substantially the same as that of human NAG and wherein the amino acid sequence is substantially as set forth in SEQ ID NO:2 or at least 80% similar to SEQ ID NO:2 and wherein the enzyme is produced by expression of a nucleic acid which encodes the enzyme or is complementary to a sequence encoding the enzyme and is carried in a vector capable of expression in a eukaryotic or prokaryotic cell, wherein the enzyme has an amino acid sequence that is 80% similar and encoded by a nucleic acid capable of hybridizing to SEQ ID NO:1 or 3

under high stringency conditions or wherein the amino acid sequence is substantially the same as that of human NAG.

Zhao et al. disclose the cloning of a human α-N-acetylglucosaminidase gene and a recombinant form of the enzyme. The reference clearly discloses that N-terminus of the enzyme starts after 23 amino acids of signal peptide and that it comprises 743 amino acids with 6 potential glycosylation sites and that a deficiency in the enzyme in humans leads to type B Sanfilippo syndrome. The above reference is not explicit on the glycosylated form of the enzyme or whether it was expressed in a prokaryotic or eukaryotic cell. The reference is also not explicit on the molecular weight of the enzyme and does not disclose the amino acid sequence of the enzyme or that the nucleotide encoding the enzyme is capable of hybridizing to SEQ ID NO:1 or 3 under high stringency conditions. However, Examiner takes the position that the human enzyme disclosed in the reference and that claimed in the instant invention are one and the same. Since the enzyme has been isolated from a human source and is a recombinant enzyme, Examiner also takes the position that the glycosylation aspect, molecular weight and the amino acid sequence including the nucleotide sequence which encodes the enzyme are all inherent characteristics and that the enzyme disclosed in the reference and that claimed are one and the same. Furthermore, as evidence that the disclosed enzyme in the above reference and that instantly claimed are one and the same, Examiner refers the applicants to the Zhao et al. PNAS USA, June 1996, Vol. 93:6101-6105 reference (and the enclosed Swissprot (accession no. P54802) amino acid sequence alignment) which discloses the amino acid sequence of the recombinant NAG which is 100% identical to SEQ ID NO:2 (see first para, column 2 on page

6101 wherein a reference is made to Zhao et al. abstract). Therefore, Zhao et al. anticipates claims 19-20, 26-29, 32, 35-36, 85, 96, 99 as written.

Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594.

Examiner regrets that the above rejection was inadvertently indicated as a rejection under 35 U.S.C. 102(a) in the previous Office action.

In response to the previous Office action, applicants have traversed the above rejection arguing that the reference discloses a potential human α-N-acetylglucosaminidase. Applicants also argue that authors of the above reference have used tryptic digests of bovine enzyme and nowhere in the abstract is disclosed that production of a recombinant form of NAG or a pharmaceutical composition comprising the same. Applicants also take the position that the reference does not teach or disclose a recombinant form of NAG and does not even disclose a cDNA or peptide sequence. Applicants also argue that Zhao et al. disclose a purified enzyme from bovine testes and there is no teaching of a recombinant enzyme, only a report for the characterization of a cDNA and genomic clone encoding the same. Examiner respectfully disagrees with all the above arguments from the applicant. First of all, applicants have now amended the claim to recite "a recombinant" enzyme, a much broader claim than before wherein it was limited to mammalian enzyme. Therefore, whether the reference discloses an enzyme

from bovine source or human source or any source is immaterial. The reference clearly characterizes the recombinant enzyme as a polypeptide with 743 amino acids with a 23 amino acid signal peptide. This information is clearly a disclosure of a recombinant enzyme. There is no reason or evidence either in the reference or in applicants argument to conclude that the enzyme disclosed in the reference is a purified enzyme and not a recombinant enzyme. While the reference is an abstract reporting the cloning of a cDNA and genomic clone as well as mutational analysis of Sanfilippo B patients using SSCP analysis of PCR amplified segments, the same reference also discloses a recombinant NAG having inherently the very same characteristics as that of the present invention as explained above. With reference to the inherency argument, Applicants indicate that the enzyme disclosed by Zhao et al. is a purified enzyme from bovine testis and that the recombinant form of the enzyme is different from tissue-derived sources. Examiner reiterates that the Zhao et al. clearly disclose that they used amino acid sequence information from the enzyme of bovine source and cloned a human enzyme and that the enzyme referred in the abstract is to the recombinant enzyme. Applicant's argument that the enzyme disclosed is a purified bovine testis enzyme is highly misplaced and misleading. In response to applicants comment that the reference does not disclose pharmaceutical composition comprising the enzyme, Examiner has excluded such claims from the above rejection. However, the rejection is maintained for other claims.

Previous rejection of claims 19-20, 26-29, 32-36, 85, 96, 99 under 35 U.S.C. 102(b) as being anticipated by Zhao(b) et al. (American Journal of Genetics, 1994, Vol. 55: A252, Abstract 1473) has been withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 21-25, 30-31, 60-67, 70-71, 97-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhao et al. (American Journal of Genetics, 1995, Vol. 57: A185, Abstract 1059). Claims 21-25, 30-31, 60-71, 97-98 are drawn to the recombinant NAG according to claim 19 expressed in a mammalian (CHO cells), yeast or insect host cells capable of N-glycosylating the recombinant enzyme wherein the recombinant NAG is also expressed as a fusion protein with another enzyme, reporter molecule, purification site and or a signal sequence, and to pharmaceutical composition comprising the above recombinant enzyme or an active fragment or derivative produced by expression of a nucleic acid encoding the enzyme and wherein the pharmaceutical composition is used in a method for treating patients suffering from NAG disorder.

Zhao et al. teach recombinant human NAG and a clone comprising the polynucleotide encoding human NAG using the amino acid sequence information of a bovine testis enzyme in conjunction with recombinant techniques such as PCR, DNA cloning and DNA sequencing. The reference also teaches that a deficiency of the above enzyme underlies the type B Sanfilippo syndrome (MPS IIIB), a mucopolysaccharide storage disorder with profound neurodegeneration

and that the above disorder is caused due to premature termination of the enzyme synthesis in those people having this disorder.

Using the teachings of references of Zhao et al., it would have been obvious to one skilled in the art at the time the invention was made to take the recombinant enzyme taught by Zhao et al. and make and use it in a pharmaceutical composition to treat the MPS IIIB disorder. Using the cDNA clone taught by the above references it would have been obvious to those skilled in the art to subclone it in any of the host cells prokaryotic or eukaryotic cells, including a mammalian, yeast or insect cell. Since it is well known in the art that eukaryotic cells have the glycosylating machinery as opposed to prokaryotic host cells, it would have been obvious to one of ordinary skill in the art to use a mammalian cell such as CHO cells in order to obtain a recombinant NAG which is N-glycosylated. Similarly, with the well known common knowledge in the art that recombinant proteins can be expressed as fusion proteins with a reporter molecule or a purification site in order to monitor either the expression of the recombinant protein or purification of the recombinant proteins, it would have been obvious to one of skill in the art to express the recombinant NAG of Zhao et al. as a fusion protein. One of ordinary skill in the art would have been motivated to do so as the above references teach the importance of the enzyme in relation to treat a human disorder. One of ordinary skill in the art would have had a reasonable expectation of success, since the above reference teaches the importance of the enzyme in human physiology and also provides a cDNA clone for the above enzyme.

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art to have performed the claimed invention.

In response to the previous Office action, applicants have traversed the above rejection by repeating and reasserting their arguments they made against the Zhao et al. reference. Furthermore, applicants argue that it would not have been obvious to those skilled in the art to subclone the cDNA taught by Zhao et al. in any of the host cells since no cDNA is provided in the reference. Examiner respectfully disagrees with such an argument. As applicants are claiming a polypeptide and not a polynucleotide sequence and as claims are not being rejected as anticipated, there is no requirement that the reference should disclose the cDNA seqeunce. Use of CHO cells or insect cells to express mammalian proteins was indeed common knowledge in the art at the time of filing of this application. In fact there are several commercial kits based on insect cells and CHO cells available for expressing mammalian proteins. Applicants also argue that it would not have been obvious to those skilled in the art to use the recombinant enzyme for treating the human disorder since no sequence for a cDNA was provided in the Zhao et al. reference. Again, Examiner reminds applicants that this is an obviousness rejection and not an anticipation rejection and therefore, there is no requirement that the actual cDNA sequence be disclosed in the reference. Furthermore, the reference clearly teaches that a deficiency of the enzyme causes the disorder. That information by itself would have been enough motivation for those skilled in the art to make a pharmaceutical preparation. Finally applicants accuse the Examiner as engaging in improper hindsight reconstruction and argue that the reference would have made those skilled in the art "to try" but not rendered the invention obvious. Examiner respectfully disagrees with such an argument and reiterates that there was no need for the Examiner to resort to hind-sight reconstruction in view of Zhao et al. PNAS USA, June 1996, Vol. 93:6101-6105 reference (and the enclosed Swissprot (accession no. P54802) amino acid

sequence alignment) which discloses the amino acid sequence of the recombinant NAG which is 100% identical to SEQ ID NO:2 (see first para, column 2 on page 6101 of Zhao(a) et al. wherein a reference is made to Zhao(b) et al.).

Claims 19-32, 35-36, 60-67, 70-71, 85, 96-99 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sasaki et al. (J.Biochem., 1991, Vol. 110(5):842-846) and the common knowledge of cloning in the art of molecular biology. Claims 19-32, 35-36, 60-67, 70-71, 85, 96-99 of the instant application are drawn to a recombinant, α-N-glucosaminidase or a fragment or a derivative of the same, expressed n mammalian cells, wherein the mammalian cell is capable of N-glycosylating the enzyme, wherein the NAG enzyme is in a glycosylated form and has a molecular weight of at least 79kDa to 89kDa when determined by SDS/PAGE and wherein the amino acid sequence of the NAG is substantially the same as that of human NAG and wherein the amino acid sequence is substantially as set forth in SEQ ID NO:2 or at least 80% similar to SEQ ID NO:2 and wherein the enzyme is produced by expression of a nucleic acid which encodes the enzyme or is complementary to a sequence encoding the enzyme and is carried in a vector capable of expression in a eukaryotic or prokaryotic cell, wherein the enzyme has an amino acid sequence that is 80% similar and encoded by a nucleic acid capable of hybridizing to SEQ ID NO:1 or 3 under high stringency conditions or wherein the amino acid sequence is substantially the same as that of human NAG. Claims are also drawn to the recombinant NAG according to claim 19 expressed in a mammalian (CHO cells), yeast or insect host cells capable of N-glycosylating the recombinant enzyme wherein the recombinant NAG is also expressed as a fusion protein with another enzyme, reporter molecule, purification site and or a signal

sequence, and to pharmaceutical composition comprising the above recombinant enzyme or an active fragment or derivative produced by expression of a nucleic acid encoding the enzyme and wherein the pharmaceutical composition is used in a method for treating patients suffering from NAG disorder.

Sasaki et al. teach a 39,000 fold purification of a human α-N-acetylglucosaminidase (NAG) from human liver. The reference teaches that the enzyme is 80 kDa size when tested by SDS/PAGE as well as other characteristics of the enzyme. The reference also teaches that a deficiency of the above enzyme is known as MPS IIIB or Sanfilippo B syndrome a severe neurodegenerative disorder in humans. However, the reference does not teach the recombinant form of the enzyme or a pharmaceutical composition comprising the enzyme or its use in the treatment of a deficiency disorder.

Using the purified enzyme provided in the above reference, it would have been obvious to those skilled in the art to obtain its amino acid sequence information by amino acid sequencing and isolate a cDNA clone from a human liver cDNA library and the recombinant form of the enzyme expressed in any of the host cells including insect cells or CHO cells as is well known in the art. Using such recombinant enzyme it would also have been obvious to those skilled in the art to make pharmaceutical compositions comprising the enzyme for treating the deficiency disorder. One of ordinary skill in the art would have been motivated to do so because a purified protein can be made in large amounts when obtained in the recombinant form. Furthermore, as the above reference teaches that a deficiency of the above enzyme leads to MPS IIIB disorder, it would have been obvious to those skilled in the art to provide the recombinant enzyme as a pharmaceutical composition for enzyme replacement therapy for those affected by

the above disorder. One of ordinary skill in the art would have a reasonable expectation of success since the above reference provides the purified enzyme and also teaches its role in MPS IIIB disorder and the art provides the methods to make a recombinant protein or a pharmaceutical composition comprising the same.

Therefore, Sasaki et al. render the above invention *prima facie* obvious to those skilled in the art.

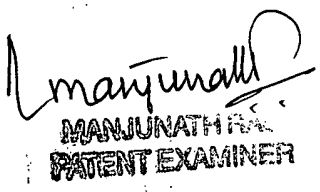
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 7:30 a.m. to 4:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is

(703) 305-3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Manjunath N. Rao
9/17/03